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Mini-Review

Graves' disease: a new era of pathophysiology-guided therapeutics

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Abstract

Graves' disease (GD) is an autoimmune entity that had an unchanged treatment paradigm for more than half a century with radioactive iodine, antithyroid drugs (ATDs), and surgery representing the mainstay of therapy, with variation in their use over time and geographic location. Hypothyroidism has been an accepted tradeoff in many cases, though recently there are increased concerns about altered quality of life in these patients. Fortunately, the last decade has seen an intense pursuit of GD's immunological mechanisms and a recalibration of classic treatment modalities focusing on thyroid preservation, as reflected in the preference for ATD as primary therapy, including its use in long-term protocols. The immune targets currently explored aim to address this gap by intervening in the TRAb lifecycle: minimizing production (eg, B-cell targeting), enhancing clearance (eg, neonatal Fc receptor inhibitors), or neutralizing its target—the TSH receptor (eg, receptor blockade). While these approaches are going through the necessary clinical trials evaluation, we are starting to see the potential for technology and artificial intelligence to make an impact on how we identify, treat, and monitor patients with GD. The combination of these approaches will likely lead to a significant individualization of GD management that will take us from the goal of normalization of thyroid levels to that of inducing long-term remission and prevention of the associated autoimmune phenomena that GD is associated with. While time is needed for these aspects to mature, the future looks bright for our GD patients and maybe soon these lessons will open new doors for our patients with Hashimoto's thyroiditis as well.

Keywords Graves' disease, therapy, FcRn inhibitor, TSHR blockade, B-cell depletion, artificial intelligence

Graves' disease (GD) is a systemic autoimmune disorder and the most common cause of hyperthyroidism, accounting for up to 80% of cases (1). The pathology is driven by TSH receptor (TSHR) autoantibodies (TRAb) that aberrantly activate the receptor, leading to excessive thyroid hormone synthesis and glandular growth (2, 3). While the thyroid gland is the primary target, the systemic nature of GD is evident in its extrathyroidal manifestations, which include thyroid eye disease (TED), pretibial dermopathy (PTD), and acropachy (4). The disease exhibits a distinct epidemiological profile, with a strong predilection for females, who are affected nearly 6 times more often than males (5, 6). It typically presents in middle-aged individuals (30-50 years of age) (7, 8), and a significant genetic component is recognized, as many patients have a family history of autoimmune thyroid disease (9, 10).

For the last 80 years, the management of GD has relied on 3 primary treatment modalities: Antithyroid drugs (ATDs), radioactive iodine (RAI), and surgical thyroidectomy (11). While these interventions effectively control hyperthyroidism, this paradigm is inherently limited, as it addresses only the peripheral hormonal consequences and, for RAI and thyroidectomy, requires the destruction of the target organ, thereby failing to rectify the underlying autoimmune process. Needless to say, surgical management can also lead to challenging complications (eg, hematoma, hypoparathyroidism, vocal cords dysfunction). Reflecting these limitations and evolving patient preferences, there has been a significant shift from historically common definitive therapies, like RAI, toward nonablative ATDs as the preferred initial treatment, with recent international surveys showing this preference is now held by over 91% of clinicians globally (12). This shift is driven by a strong desire to preserve the thyroid gland and avoid the risks, including radiation exposure and subsequent lifelong hypothyroidism, inherent to ablative therapies (13). However, significant challenges remain across all conventional options, including ATD-related toxicity, low remission rates, and the failure to address extrathyroidal manifestations (14).

It is this broader therapeutic gap that has expanded the goals of modern GD management beyond simple hormonal control or permanent thyroid destruction, shifting the focus to directly

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targeting the fundamental autoimmune process. To that end, this review introduces a pathophysiology-centric framework that organizes investigational agents by their strategic intervention in the TRAb lifecycle: production, clearance, or target neutralization. This, we hope, is a more clinically intuitive framework for endocrinologists.

The current therapeutic landscape: successes, limitations, and unmet needs

Conventional treatments

When ATDs are chosen as the primary therapy for GD, the goal of a standard 12-18 month course is to induce durable remission, but this is only successful in up to 50% of patients (15). Consequently, a primary clinical challenge is the high recurrence rate following ATD withdrawal. Effective risk stratification at diagnosis is therefore crucial for guiding initial treatment discussions, if the goal is to stop all treatments after standard ATD therapy.

While individual risk factors for recurrence—such as younger age (<40 years), a large goiter, high baseline free thyroxine (FT4) and TRAb levels, and active smoking status—are well-recognized (16, 17), validated scoring systems provide a more integrated approach (18, 19). The most widely used tool is the Graves' Recurrent Events After Therapy score, which integrates these variables to classify patients into low (Class I), intermediate (Class II), or high (Class III) risk categories for recurrence (20). This allows clinicians to better counsel patients on the likelihood of remission with ATDs vs the potential need for definitive therapy. Although other more complex models incorporating genetic markers or shear elastography have been proposed (21-23), they have not been sufficiently validated and are not yet widely available for routine clinical use. Throughout treatment, serial TRAb measurement remains the most robust tool for monitoring immunological response, as normalization of titers by the end of therapy is strongly predictive of successful remission (24). Additionally, the ability to maintain euthyroidism on a low maintenance dose of methimazole (MMI, eg, ≤5 mg/day) before discontinuation is also associated with a higher likelihood of remission and a lower risk of relapse (25). For patients who relapse or remain at high risk (eg, persistent TRAb), long-term ATD therapy has emerged as a validated alternative to definitive treatment (26). This strategy involves continuing a low-dose ATD for an extended period, often 5 years or more, to achieve higher remission rates (over 80%) (27). While effective, this strategy requires sustained patient adherence and carries the burden of continuous monitoring.

When ATD therapy fails to induce remission, is contraindicated, or when a patient prefers a permanent solution, definitive therapies like RAI and thyroidectomy are considered (11). RAI offers an effective, nonsurgical ablative option. Given the high recurrence rates associated with subablative dosing (28), the therapeutic goal is to induce definitive hypothyroidism. While it remains a suitable therapy for women planning a future pregnancy, provided they wait at least 6 months after administration, its use in this population requires careful counseling. A primary concern is that RAI can cause a marked and persistent increase in maternal TRAb levels, which cross the placenta and create a significant risk for fetal and neonatal thyrotoxicosis (29, 30). Its other primary limitations include strict contraindications in pregnancy, lactation, and moderate to severe active TED. Furthermore, RAI is associated with a risk of de novo TED occurrence or the progression of preexisting mild TED in ∼15% of patients (31, 32). This risk is elevated in those with known risk factors like smoking and high TSHR antibody levels, and can be ameliorated with a short course (6-12 weeks) of low-dose oral steroid prophylaxis (33).

Surgical thyroidectomy is often the preferred therapy in cases where RAI is less desirable, such as for patients with large goiters causing compressive symptoms, coexisting suspicious thyroid nodules, or significant ophthalmopathy (11). It provides the most rapid and definitive cure with the lowest rate of disease recurrence and is the treatment of choice for women planning pregnancy within 6 months or those with concerns for neonatal thyrotoxicosis (high TRAb). Although surgery avoids the specific ocular risks of RAI, its primary drawbacks include the inherent risks of the procedure, such as permanent hypoparathyroidism and recurrent laryngeal nerve injury, which are significantly reduced when performed by a high-volume surgeon (34). Both RAI and surgery lead to lifelong thyroid hormone replacement, and this treatment should be discussed upfront, with its goals and monitoring requirements.

The burden of pharmacologic toxicity

Although ATDs are generally considered safe, with major adverse events (such as agranulocytosis, severe hepatotoxicity, and vasculitis) occurring in fewer than 1% of cases, their clinical utility as first-line therapy can be limited by pharmacological toxicities (35). Even milder reactions, like rash, may impair patient compliance or lead to treatment discontinuation, particularly as adverse events most often occur within the first 3 months of therapy. Significant differences exist in the risk profiles of the 2 main agents. Methimazole is preferred for most patients due to superior efficacy and lower risk of severe hepatotoxicity, although its most significant but fortunately rare complication is agranulocytosis (0.2-0.5%) (36). Propylthiouracil (PTU) is reserved for the first trimester of pregnancy (due to lower teratogenic risk) and thyroid storm. While PTU has been traditionally recommended in storm for its ability to block peripheral T4-to-T3 conversion, recent large-scale comparative studies, including nationwide data from Japan, show no significant difference in mortality or other major clinical outcomes between PTU and MMI (37, 38). PTU also carries a higher risk of severe liver injury and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (39, 40).

Defining unmet needs and expanded therapeutic goals

While current therapies effectively address hyperthyroidism, they fail to rectify the underlying systemic autoimmune process, the production of pathogenic TRAb. This fundamental failure, coupled with the limitations detailed above, creates significant unmet

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clinical needs. Addressing these limitations requires a shift in therapeutic ambition: moving beyond transient biochemical control to achieving durable elimination or inactivation of pathogenic TRAb, leading to sustained drug-free remission. Such a goal would also prioritize the prevention and treatment of extrathyroidal manifestations like TED and PTD. As these novel therapies emerge, a new clinical challenge will be the appropriate selection of patients who may still benefit from traditional treatments versus those who would be better candidates for these newer alternatives (Fig. 1).

A pathophysiology-guided framework for novel therapeutics

Broad immunomodulation

There have been many attempts over the years to achieve a broad inhibition of the immune system, as is done for other autoimmune disorders (Fig. 2). Intravenous (IV) methylprednisolone (41), methotrexate (42), azathioprine (42), and rituximab (RTX) (43, 44) are clearly known to inhibit the immune system and exhibited some marginal beneficial GD effects in these trials. In this context, MMI has been considered by some to have an immunomodulatory role (45, 46), though the clinical evidence is not able to separate that effect from the simple passage of time. The challenge with pursuing these broad immunosuppressive therapies has been their limited and transient benefit, combined with a significant side-effect profile that could not compete favorably with the use of MMI or with ablative therapies followed by levothyroxine treatment.

Modulating the production of TSHR autoantibodies

Interrupting B–T-cell costimulation

Stimulation of CD40 on the surface of B cells is essential for the activation of the immune response, including in autoimmunity (Table 1). Therefore abrogating this interaction led to germ cell depletion and suppression of murine thyroiditis in animal models of GD (47, 48). In view of this evidence, there has been 1 open-label clinical trial attempting to inhibit CD40–CD40 ligand interaction with a CD40 ligand blocker (iscalimab) (49). Of 15 patients with new GD diagnosis, 7 responded clinically and biochemically, and it was concluded that efficacy was strongly correlated with baseline TRAb values. Whether genetic polymorphism in CD40 gene plays a role in GD presentation and therapeutic response remains unknown, given conflicting genetic study results and limited human trial data (50-52). Currently, a separate CD40 ligand inhibitor (Lu AG22515) is being evaluated in a phase 1 open-label study (NCT06557850) for TED patients, and those results could certainly serve as a basis for revisiting this route in patients with GD.

B-cell depletion

The role of B-cell depletion in adults with GD has been tested by 2 European groups utilizing RTX as a CD20-targeting agent (44). The El Fassi group identified the rate of remission after RTX (combined with only 3 months of MMI) at 40% 2 years later, similar to the result seen after a full 18 months of ATD therapy. While thyroid stimulating immunoglobulins (TSI) decreased with RTX therapy and the drug has been tested more extensively in TED, to our knowledge, it has not been pursued further for GD in adults, even though discussions about other B-cell targeting approaches are ongoing. As such the targeting of CD3–CD19/CD20 (ie, teclistamab) has come to the fore. While it has been pursued for hematological malignancies (53), recent work in a heterogeneous group of autoimmune disorders resistant to classical therapy describes a broad benefit in this area. Specifically, in one case of GD with TED, a significant decrease in proptosis was noted along with apparent improvement in hyperthyroidism (54). Finally, chimeric antigen receptor (CAR)-T cell therapy, which also focuses on CD19 expression, warrants mention. It should be noted, though, that while CD19 seems to be present in the population that encompasses memory cells, it is gradually lost as memory B cells differentiate into plasma cells. Currently, we are aware of a single phase one study focusing on allogeneic anti-CD19 CAR-T cell therapy for refractory GD, ongoing in China (Clinicaltrials.Gov NCT 07129642). This approach implies (1) collection of a patient's T cells, (2) their ex vivo modification to express a CAR that can target CD19 B cells and at the same time activate cytokines leading to cell destruction; (3) ex vivo amplification and purity control, and then (4) readministration to the patient. Given the complexity associated with this process it is likely that if this approach is successful, it will be under extensive scrutiny as to which GD patients it would be beneficial, in comparison with alternative therapies.

Restoring immune tolerance (antigen-specific immunotherapy)

The fact that TSHR becomes an autoantigen in GD patients has led to the idea of replicating the desensitization approach used by our colleagues in allergology. Peptides from the large extracellular component of TSHR have been synthesized (apitopes) leading to the development of ATX-GD-59 (55). This compound was administered subcutaneously (SQ) in ascending doses to patients with mild GD in a phase 1 trial (56). Seven of 10 patients had improvement in thyroid levels, correlating with decreasing TRAb, but remission was noted in only 2 patients. The intervention was well tolerated but there are no ongoing trials exploring this route at present (the only follow-up trial, NCT06240455, is currently suspended).

Enhancing the clearance of circulating TSHR autoantibodies

Neonatal Fc receptor inhibitors

This class of agents binds and inhibits the neonatal Fc receptor (FcRn) protein (Table 1). This protein acts by protecting IgG in its intracellular phase from lysosomal degradation, extending the half-life of IgG to approximately 3 weeks. As a result of blocking FcRn from providing its protective role there is an increase lysosomal degradation of IgG with a subsequent decrease in its overall as well as TRAb titers by 50-75% (57). The agents that have advanced to phase 2/3 randomized control trials (RCTs) in GD/TED are batoclimab and its next generation iteration,

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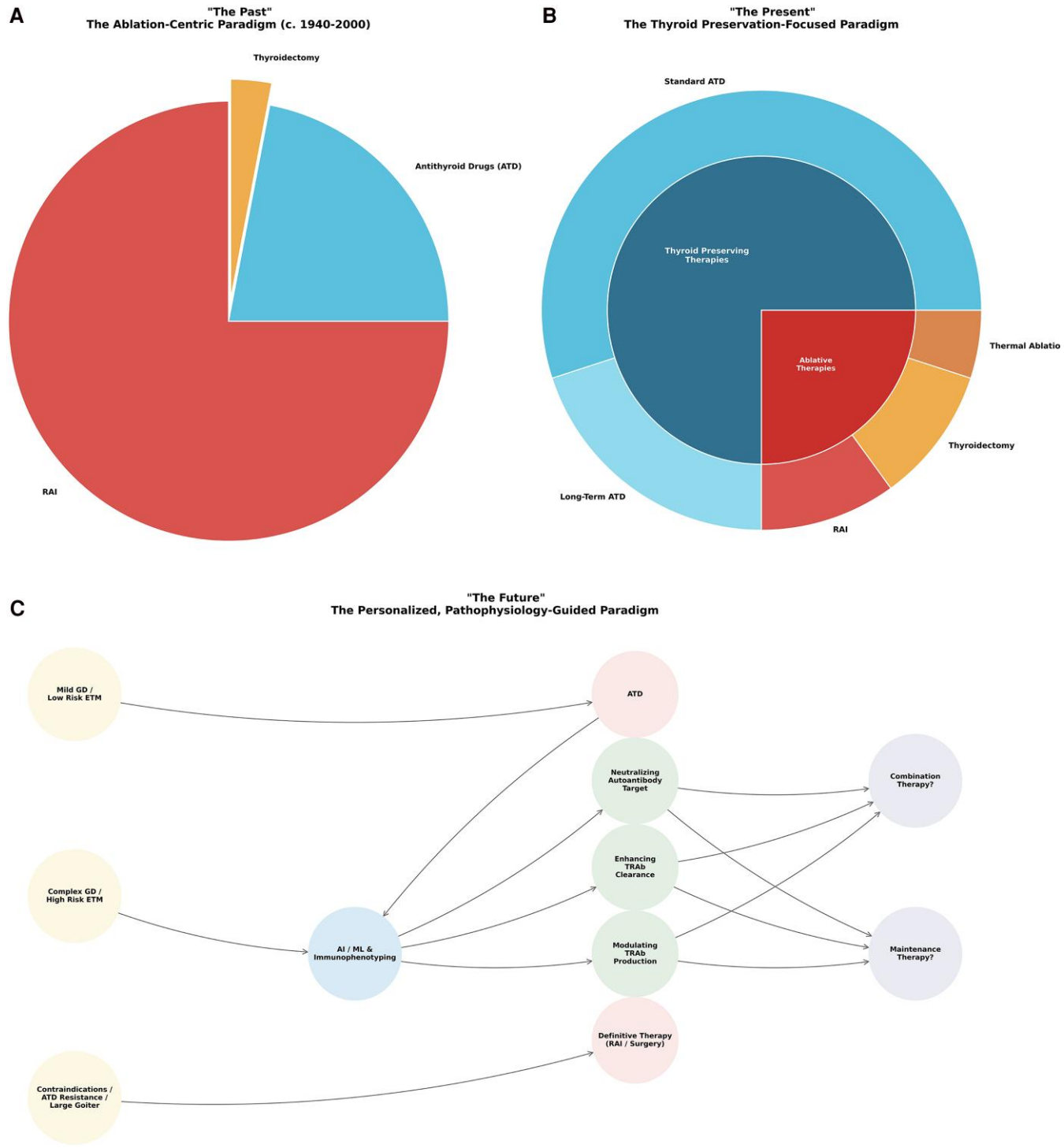

Figure 1 The evolution of the therapeutic landscape for GD. (A) Represents "The Past," an ablation-centric model dominated by RAI. (B) Illustrates "The Present," a thyroid preservation-focused approach with a clear shift toward ATD use. (C) Depicts "The Future," a personalized, pathophysiology-guided model where patient stratification and AI direct the use of specific therapies.

IMVT1402, and efgartigimod. Batoclimab achieved a 56% rate of euthyroidism off ATD after 12 weeks of therapy, with a residual response of 36% at 24 weeks, as the dose was halved (58). IMVT1402 is currently being studied for GD in 2 parallel RCTs (NCT07018323 amd NCT06727604) and is expected to avoid the lipid changes that have plagued batoclimab (59). Efgartigimod, a drug already approved for generalized myasthenia gravis, is also being studied in 2 parallel RCTs (NCT06307626 and NCT06307613), and both these agents are hoping to report their results in 2027.

Molecular degraders of extracellular molecules

Molecular degraders of extracellular (MoDE) proteins represent a novel approach to clearing circulating IgG and, implicitly, TRAb. These bifunctional molecules work by simultaneously binding a specific extracellular target, in this case IgG, and a cell surface

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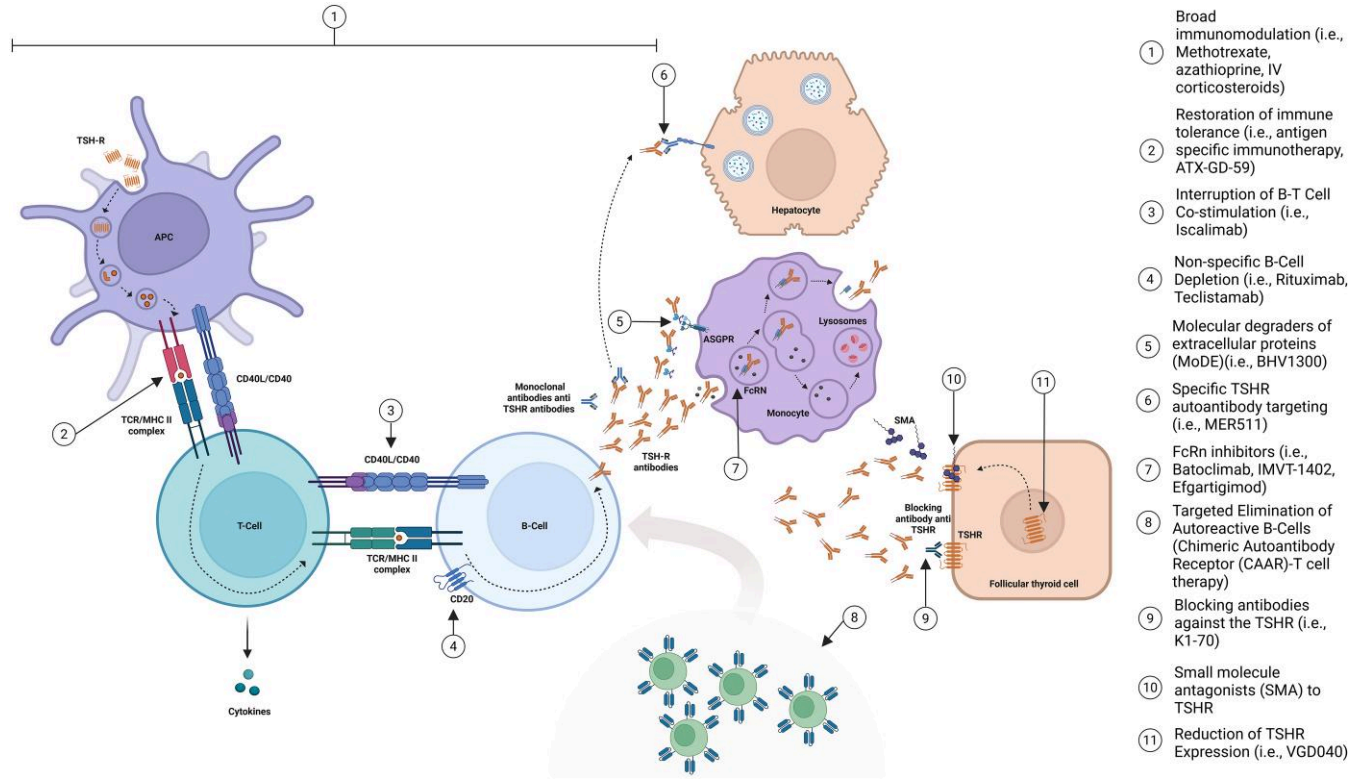
TSH-R
APC
CD40L/CD40
TCR/MHC II complex
T-Cell
B-Cell
CD20
Cytokines
Monoclonal antibodies anti TSHR antibodies
TSH-R antibodies
Hepatocyte
ASGPR
Lysosomes
FcRN
Monocyte
SMA
Blocking antibody anti TSHR
TSHR
Follicular thyroid cell
1 Broad immunomodulation (i.e., Methotrexate, azathioprine, IV corticosteroids)
2 Restoration of immune tolerance (i.e., antigen specific immunotherapy, ATX-GD-59)
3 Interruption of B-T Cell Co-stimulation (i.e., Iscalimab)
4 Non-specific B-Cell Depletion (i.e., Rituximab, Teclistamab)
5 Molecular degraders of extracellular proteins (MoDE)(i.e., BHV1300)
6 Specific TSHR autoantibody targeting (i.e., MER511)
7 FcRn inhibitors (i.e., Batoclimab, IMVT-1402, Efgartigimod)
8 Targeted Elimination of Autoreactive B-Cells (Chimeric Autoantibody Receptor (CAAR)-T cell therapy)
9 Blocking antibodies against the TSHR (i.e., K1-70)
10 Small molecule antagonists (SMA) to TSHR
11 Reduction of TSHR Expression (i.e., VGD040)

Figure 2 Pathophysiology-guided therapeutic targets in GD. This figure illustrates the key cellular interactions and molecular pathways involved in the pathogenesis of GD, highlighting novel therapeutic strategies categorized by their mechanism of action.

scavenger receptor, such as the asialoglycoprotein receptor in the liver. This bridging facilitates the internalization and subsequent lysosomal degradation of the target protein.

The best known is BHV1300, a small molecule MoDE that achieved a reduction of up to 84% in IgG 1, 2 and 4 in phase 1 healthy volunteer studies. Interestingly, it spared IgG3, which is thought to be less involved in autoimmune antibody development and to have a more potent anti-infectious role (60). A phase 1 study targeting GD patients (NCT06980649) was just initiated, with expected completion by early 2026.

Specific TSHR autoantibody targeting

Results presented in June of 2025 at the annual meeting of the Endocrine Society indicated the development of a monoclonal antibody (MER511) that would specifically target TRAb (61). This antibody has a component that mimics TSHR (for capturing TRAb) and a component that is able to bind FcγRIIB on the surface of the sinusoidal hepatocyte system, thus allowing it to be cleared, along with its attached TRAb. Meaningfully, the TSHR-like component does not bind endogenous TSH in laboratory studies, theoretically allowing for restoration of normal thyroid function with this therapy. A phase 1 study in GD patients is expected to start early 2026.

Neutralizing the autoantibody target (effector-level intervention)

Direct TSHR blockade

Antibodies blocking the TSHR have been identified back in 2010 by Evans et al (62) (Table 1). That work identified in the same patient both a stimulating TSHR antibody (M22) and a blocking antibody to the TSHR (K1-70). A phase 1 study with K1-70 in GD patients, reported in 2022, identified a good safety profile and the ability of this agent to rapidly induce hypothyroidism, despite ongoing TSHR stimulation (63). Of note, 6/8 patients with TED had improvement in their TED features during that trial. An interesting endorsement of this antibody's bioactivity came from its compassionate use in a patient with metastatic follicular thyroid carcinoma, GD, and TED (64). The drug was able to block the high titer of TRAb and induce both temporary stabilization of the thyroid cancer as well as improvement in the patient's eye disease. A second phase 1 trial was recently completed in Japan, and it produced similar results (65), with reduction in proptosis in several patients with inactive TED. This drug is expected to induce hypothyroidism at therapeutic doses and replacement therapy with levothyroxine will likely be part of the treatment paradigm, if it reaches clinical practice. The unknown element here is the impact of TSHR blockade on nonthyroidal tissues, as we know that TSHR is expressed in many organs (eg, bone, skeletal muscle, heart, adipose tissue). Careful monitoring of these systems will be required in upcoming clinical trials.

Small molecule antagonists (SMAs) to TSHR have also been explored for the last decade, as potential orally administered agents to block conformational changes in the transmembrane domain of TSHR, irrespective of TRAb presence. A number of them have been reported in laboratory cell culture studies (66-69), but unfortunately none have advanced to human studies. Their main challenge remains ensuring adequate specificity to the TSHR while avoiding interference with the homologous FSH and LH receptors.

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Table 1 Summary of novel therapeutics for GD

Mechanism category	Subclass	Molecular target	Agent	Completed evaluations (for GD, except phase I)	Comments, challenges, and plans[a]
Modulating TRAb production	Interrupting B–T-cell costimulation	CD40 (on B cells)/CD40 ligand (CD154) (on T cells)	Iscalimab (CFZ-533)	Phase II	Nonspecific immunosuppression. No active plans.
		CD40 ligand (CD154)	Lu AG22515	No data	Nonspecific immunosuppression. Phase 1 ongoing for TED.
	B-cell depletion	CD20 (on B cells)	RTX	Phase II	Prolonged B-cell depletion. Nonspecific immunosuppression. No registered trials (plans for trial in teenagers from BTF[c]).
		CD3 (on T cells) and CD19/CD20 (on B cells)	Teclistamab	Phase I (for MM[b])	No active plans.
		CD19 (on B cells/plasmablasts)	Allogeneic anti-CD19 CAR-T cell therapy	No data	Nonspecific immunosuppression. Phase I ongoing for GD.
	Restoring immune tolerance	TSHR peptides (antigen-specific immunotherapy)	ATX-GD-59 (“apitopes”)	Phase I	Very specific. No active plans (ongoing trial is suspended).
Enhancing TRAb clearance	FcRn inhibition	FcRn	Batoclimab (HL161)	Phase II (PoC)	Nonselective IgG depletion. Cholesterol elevation. Phase III (for TED) ongoing.
			IMVT-1402	Phase I	Nonselective IgG depletion. Phase 2b (for GD) enrolling.
			Efgartigimod (ARGX-113)	Phase I	Nonselective IgG depletion. Phase III (for TED) ongoing.
	MoDE	IgG1, 2, 4 (via hepatic receptors M6PR and ASGPR)	BHV-1300	No data	Selective IgG1, 2, and 4 depletion. Phase I (recruiting).
	Specific TRAb targeting	TRAb (via TSHR-mimetic capture and FcγRIIB clearance)	MER511	No data	Very specific. No registered trials.
Neutralizing TRAb target	Direct TSHR blockade (monoclonal antibody)	TSHR (allosteric antagonist)	K1-70	Phase I	Very specific. Off-target TSHR blockade. Likely “block-and-replace” strategy. No registered trials.
	Direct TSHR blockade (SMAs)	TSHR (transmembrane domain)	Various preclinical agents (eg, NCGC00229600, SYD5115)	No data	Oral and adjustable dosing. Uncertain specificity (FSH receptor/LH receptor cross-over?). No registered trials.
	Reducing TSHR expression	TSHR nascent protein (via ER translocation)	VGD040 (CADA compound)	No data	Uncertain protein specificity. Off-target TSHR blockade. No registered trials.

Refer to the text for the full set of acronyms/abbreviations.
Abbreviation: BTF, British Thyroid Foundation.
[a]Based on ClinicalTrials.gov information and public information.
[b]Multiple myeloma.
[c]BTF announced a plan for RTX trial in teenagers to start in 2025 (https://www.btf-thyroid.org/rituximab-in-graves-disease).

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Reducing TSHR expression

Recent work by Krieger et al has highlighted a novel potential pathway to diminish the availability of TSHR on the surface of thyroid follicular cells (70). They have tested a cyclotriazadisulfonamide (CADA) compound (VGD040) that in cell culture of human thyrocytes was able to inhibit the process of endoplasmic reticulum translocation of TSHR and thus diminish TSHR transfer to the cell membrane. In animal models this approach led to a decrease in T4 values in response to TSH stimulation. Extensive work will be needed to define and refine the specificity of this approach before clinical trials can be considered.

Novel nonsurgical ablative therapies

RAI has been the primary nonsurgical ablative modality for decades, but persistent concerns regarding radiation exposure have fueled interest in alternatives. Thermal ablation techniques have been investigated as nonradiation alternatives to destroy thyroid parenchyma and induce euthyroidism. A group from Hong Kong reported on 30 patients that did not have a clear surgical indication for persistent or recurrent GD and were treated with radiofrequency ablation (RFA) (71). After 2 years of follow-up, 57% of patients were euthyroid or hypothyroid, and the best predictor of success was a preablation thyroid volume of <20 mL. The use of microwave ablation led to similar results, with a small study (8 patients) reporting 62% success rate at 12 months (72). The same group from Hong Kong also explored high-intensity focused ultrasound, finding that 2 years after the ablation of most thyroid parenchyma the success rate was 59% (73). It is also important to consider the study that compared the quality of life (QOL) of individuals treated with 1 of the 3 ablative therapies, which found that 2 years later, RFA-treated patients had significantly better outcomes on a thyroid-specific QOL instrument, compared with RAI or surgery (74). It is notable, however, that cases of GD have been reported after RFA (75) or microwave ablation (76) for benign thyroid nodules, within a few months after the procedure. Furthermore, the experience with subtotal thyroidectomy suggests that the persistence of TRAb will likely lead to ongoing stimulation of residual thyroid parenchyma, with an increase in the recurrence rate over longer-term follow-up. Therefore, these ablative approaches are probably best reserved for a research environment only at this time.

Microbiome-based strategies: the gut–thyroid axis

For more than a decade, there has been an interest in the relationship between the composition of gut microbiome and the development of thyroid autoimmunity, both GD and TED. The current working hypothesis is that alterations in the ratios of certain commensal bacteria can induce changes in immune cell populations (77, 78). In a murine model of GD and TED, it was noted that the clinical phenotype correlated with a decreased prevalence of *Bacteroides* species (79). After encouraging murine data (79, 80), the INDIGO study in humans did reveal an apparent microbiome signature of GD and TED vs controls (81). Unfortunately, that was different than the signature identified in Asian studies (82, 83) indicating that culture and environment (diet in particular) are likely to have a significant impact on gut microbiome, independent of thyroid autoimmunity. Hopefully further studies will bring clarity to this field and answer the question of the potential benefit of regulating gut microbiome in order to reverse the consequences of thyroid autoimmunity.

Evolving the paradigm of GD management

The role of technology in personalized care

The integration of digital health and artificial intelligence (AI) offers a path toward proactive GD management, though these applications remain largely investigational (84). Preliminary studies suggest that machine learning models can utilize continuous heart rate data from wearable devices to detect thyrotoxicosis with high sensitivity (86.1%) and specificity (up to 98.3%), potentially offering a tool for early detection of hyperthyroid flares (85,86) .

Beyond monitoring, AI is being explored to enhance diagnostic and prognostic accuracy. Deep learning models have demonstrated the ability to differentiate GD from thyroiditis on ultrasonography and predict relapse risk after ATD withdrawal using baseline clinical characteristics (87, 88). Furthermore, multimodal AI models are being investigated to grade and predict treatment responses in TED through the analysis of orbital imaging and facial photographs (89, 90). While these technologies represent a shift toward a more personalized management paradigm, their current clinical utility is constrained by the need for prospective validation, data standardization, and regulatory approval.

Integrating novel therapies into clinical practice

As novel therapies make their way into practice, we still expect that the majority of patients will be started on ATDs treatment, as is the practice now. However, in certain subgroups that are yet to be defined, the utilization of a treatment aimed to eliminate TRAb or block its action on the receptor would likely be considered. That transition will certainly be a management challenge for a while. The speed with which ATDs treatment would be tapered will depend on the speed with which the new drug's mechanism of action takes over. Subsequently, some of these drugs (ie, TSHR blockers) will require the addition of levothyroxine for a period of time, analogous to the occasionally employed regimen of block and replace. As we have seen with ATDs, the duration of therapy is not a fixed one. Will maintenance therapy be required? Will TRAb/TSI monitoring be the guide for that?

Separately, the administration of these drugs will likely be parenteral, either IV or SQ, at intervals between weekly to monthly or even further apart. Identifying resources for administration or

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Table 2 Impact of novel therapies on management in special clinical scenarios

Scenario	Current key management principles (guideline based)	Potential impact of novel therapies
GD + TED/PTD	• Parallel organ-specific management • GD: ATD/surgery • TED: IVGCs/teprotumumab • PTD: topical/lesional steroids +/− other therapies	• Early disease: Rapid control of hyperthyroidism + TRAb elimination/blockade for TED/PTD prevention • TED/PTD present: TRAb targeting to control TED/PTD; combination with IGF-1R blocker? • Need for maintenance therapy?
Preconception and pregnancy	• Achieve euthyroidism preconception. • PTU first/MMI second to third trimester if needed[a] • TRAb testing by 18-22 and again at 30-34 weeks to inform risk of fetal/neonatal thyrotoxicosis[b]	• Aim to eliminate TRAb preconception • None of the novel therapies have data on pregnancy impact • FcRn inhibitors, MoDE, and TSHR blockers will likely be contraindicated during pregnancy due to mechanism of action
Thyroid storm	• Clinical diagnosis with multisystem failure • Multimodal intensive supportive care + thyroid targeted therapy • Plasmapheresis as potential bridge to surgery	• Rapid-acting TSHR antagonists could combine with TRAb clearance agents for fast thyroid level normalization

Refer to the text for the full set of acronyms/abbreviations.
Abbreviation: IVGCs, IV glucocorticoids.
[a]GD can enter in remission during pregnancy, and ATDs can therefore be discontinued. Monthly monitoring can help in this respect.
[b]TRAb >5 IU/L is a cutoff for increased risk and need for intense monitoring.

training of patients for self-administration will be essential for the feasibility of using these new agents.

The cost of these agents will certainly exceed that of ATDs and RAI. The financial perspective will be important to consider, having a broad view not only on the ability to control hyperthyroidism but also the ability to treat or prevent extrathyroidal manifestations of thyroid autoimmunity and patients' QOL.

Finally, the safety of these drugs will play out in a different manner than our well-established therapeutic choices. What is the clinical impact of a long-term decrease in IgG, of increased circulating immune complexes looking for hepatic degradation, of blocking TSHR systemically, etc., will have to be understood and monitored adequately. All of us endocrinologists, along with our colleagues from primary care, will have to be willing to learn and understand the profile of these agents in order to serve our patients well.

Management in special populations and scenarios

An integrated approach to thyroid and extrathyroidal disease

While radiological changes of TED are present in most GD patients, the disease is clinically manifest only in about a third of this population (91), while PTD affects <5% of GD patients (92) (Table 2). The mechanisms behind these 2 GD-associated entities are incompletely defined but likely related to TRAb-induced fibroblast stimulation with subsequent adipogenesis, deposition of hyaluronic acid, and fibrosis (91). Furthermore, we know of cross-over signaling between TSHR and insulin growth factor 1 receptor (IGF-1R) on fibroblasts, a potent mechanism that leads to the clinical changes in TED and explains the highly effective therapy with IGF-1R inhibition (93). We have some limited evidence that the same approach is beneficial for PTD (94), but this approach does not influence thyroid hormone levels. On the other hand, some of the therapies described earlier could provide overarching treatment for hyperthyroidism, TED, and PTD. We would expect that targeting TRAb should offer the possibility of TED/PTD prevention or improvement, in their early pre-fibrotic phase. Therefore, the agents that we described in the pathophysiology-guided framework above could be evaluated for these conditions.

Preconception counseling and management in pregnancy

Preconception counseling for women with GD is critical, as uncontrolled hyperthyroidism is linked to miscarriage, preterm birth, and other poor outcomes (95, 96). Effective contraception is advised until a stable euthyroid state is achieved (97). Counseling should include a discussion of all therapeutic options. Definitive therapy with thyroidectomy or RAI before pregnancy can prevent the need for ATD exposure during gestation. Thyroidectomy is often the preferred definitive option in this group, as RAI is contraindicated during pregnancy, and conception must be delayed for at least 6 months after such ablation (11). Furthermore, a primary concern with using RAI for women planning pregnancy is that it can cause a marked and persistent increase in maternal TRAb levels, which cross the placenta and create a significant risk for fetal and neonatal thyrotoxicosis (29).

If ATDs are the chosen therapy, patients must be counseled on the teratogenic risks and the standard management plan: PTU is the preferred agent during the first trimester to avoid MMI-associated embryopathy, followed by a switch to MMI in the second trimester to reduce the risk of PTU-induced hepatotoxicity (39, 97). During pregnancy, management requires careful monitoring based on this trimester-specific ATD approach, with thyroid function tests recommended approximately every 4-6 weeks. The biochemical

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goal is to maintain the mother's free T4 or total T4 at or just above the upper limit of the pregnancy-specific reference range, using the lowest possible ATD dose. Maternal TSH often remains suppressed, and attempting to normalize it risks overtreating the mother and inducing fetal hypothyroidism (29). Finally, TRAb levels must be monitored during pregnancy. TRAb can cross the placenta and stimulate the fetal thyroid, causing fetal or neonatal hyperthyroidism (98). If maternal TRAb levels are high, fetal ultrasound monitoring is warranted to screen for signs of fetal thyrotoxicosis, such as goiter, tachycardia, or hydrops. This is a critical concern even in women who are euthyroid after definitive treatment (RAI or surgery), as they may still have high circulating TRAb levels. In these cases, the mother may need to take ATDs if there are signs of fetal thyrotoxicosis (99). Management extends into the postpartum period, where the risk of relapse is high and continued monitoring is required (100). For mothers who choose to breastfeed, MMI (in doses up to 20 mg/day) is considered safe, as it passes minimally into breast milk (101). This complex management paradigm highlights a significant unmet need—the lack of an effective TRAb-eliminating therapy—which hopefully the novel, targeted immunotherapies currently in development might be able to tackle.

Thyroid storm

Occasionally GD leads to extreme hyperthyroidism with multiorgan system involvement, thyroid storm. The diagnosis of this complication is a clinical one, and there are 2 instruments that are helpful for this assessment, the Burch–Wartofsky Point Scale (102) and the Japan Thyroid Association Diagnostic System (103). Once the diagnosis is established, the urgency of the therapy imposes itself given the 20% mortality still associated with this condition (104). The treatment should be a multifaceted approach undertaken in an intensive care unit setting and, given its complexity, we defer its description to the focused reviews available in the literature (105). The only mention that we will make relates to the emergence of plasmapheresis as a highly effective modality for rapidly lowering thyroid hormone levels in preparation for thyroidectomy (106) and the possibility that TRAb capture (3.3.3.) combined with TSHR blockade (3.4.1.) might revolutionize the treatment of this dreaded complication.

Conclusions

Thyroid preservation has become the main choice when selecting between available GD therapies. This is a fortuitous trend that will allow patients to take advantage of upcoming novel therapies since, after decades of stagnation, the field of GD is finally seeing the development of agents dedicated specifically to this autoimmune pathology. Their main goal is to minimize or eliminate the autoimmune response to TSHR. This will obviously have potential impact on the whole field of thyroid autoimmunity, including TED and PTD, from prevention to therapy. Furthermore, the spectrum of pathophysiological targets for these agents is impressive and likely will open the door for an individualized therapy based on disease phenotypes and patients' comorbidities. This is a powerful wave that we can hopefully surf well all the way to the desired shore of normal thyroid function without long-term pharmacotherapy.

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Figure 2 was created in BioRender. Stan and Tobon (2026) https://BioRender.com/qjv81u3.

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Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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